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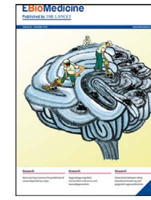

Commentary

Sphingosine 1-phosphate escapes the Catch-22 of sepsis prevention and mitigation therapies

Victoria A. Blaho*

Immunity and Pathogenesis Program, Sanford Burnham Prebys Medical Discovery Institute, La Jolla, CA 92037, U.S.A.

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Sepsis is defined as life-threatening organ dysfunction as a consequence of a dysregulated host immune response to infection and is the leading cause of mortality across the globe [1]. Septic organ dysfunction leads to a 2-2•5 times greater risk of death, and patients that progress to septic shock have hospital mortality rates greater than 40%. With few options available for prevention or treatment, antibiotics and supportive therapies are initiated empirically.

The excessive amplification of proinflammatory cytokines, and other inflammatory mediators, that are essential for the deterioration of organ function is called a cytokine storm, a relatively obscure term until recently. The conspicuous inflammation of a sepsis cytokine storm has been unsuccessfully targeted in clinical trials, particularly by antibodies that inhibit cytokine signaling [2]. In some cases, cytokine suppressive therapies increased sepsis mortality. A similar barrier exists to utilizing another drug in sepsis, the anthracycline epirubicin [3]. Mechanistically, epirubicin could prevent or mitigate early sepsis hormetically by activating DNA damage responses and autophagy pathways, reducing proinflammatory cytokines and markers of tissue damage. While 0•6 μg/kg epirubicin administration in combination with a broad-spectrum antibiotic could extend the therapeutic window up to 24 h beyond sepsis induction, higher doses dramatically increased sepsis lethality.

In this issue of *EBioMedicine*, Weigel and colleagues demonstrate that the beneficial aspects of epirubicin treatment in experimental sepsis can be ascribed to modulation of sphingosine 1-phosphate (S1P) metabolic and signaling pathways and propose that their direct modulation may be more efficacious and less fraught [4]. They report that 0•6 μg/kg epirubicin significantly suppressed upregulation of the S1P degradative enzyme S1P lyase (SPL) in lung tissue and peripheral blood cells of mice with experimental sepsis, increasing local S1P concentrations. SPL expression and activity are responsive to cell stress, and its catabolism of S1P decreases local S1P concentrations and regulates autophagy in a cell type-specific manner [5]. S1P is a critical bioactive lipid regulator of the vascular and immune systems, which are both integral to sepsis development. Specific S1P signals are transduced by cognate G protein-coupled receptors, $S1P_{1\text{-}5}$, responding to S1P concentrations tightly controlled by specific synthetic and catabolic enzymes [6].

Plasma S1P concentrations of sepsis patients inversely correlate with both disease severity and mortality, a relationship also seen in experimental sepsis [4,7]. Weigel, et al. also found that mRNA for SPL was significantly increased in peripheral blood cells of sepsis patients. Administration of the SPL inhibitor THI (2-acetyl-5-tetrahydroxybutyl imidazole), a component of caramel color III food coloring, recapitulated the suppressive effects of epirubicin on pro-inflammatory markers while significantly increasing plasma and lung S1P concentrations concomitant with decreased mortality. Using $S1P_3$-specific agonists, Weigel, et al. demonstrate that signaling by this receptor may be key to S1P-mediated suppression of inflammation in experimental sepsis.

The S1P pathway has become an attractive therapeutic target for numerous diseases, many of autoimmune origin. Several S1P receptor modulators are FDA approved with many more in development. Likewise, SPL-specific modulators are of particular interest in pulmonary and renal diseases. Whether inhibition of SPL or specific agonism of $S1P_3$ are beneficial or detrimental in human sepsis will depend upon the organs most affected, underlying comorbidities, instigating infectious organism, and patient age. The last two factors—pathogen and patient age—are of particular importance at this time. There are over 4 million neonatal and pediatric sepsis cases per year worldwide with 10–20% mortality rates [8]. Conversely, elderly patients over the age of 80 have a sepsis mortality rate over 50% [9]. While our understanding of COVID-19, the disease caused by infection with the SARS-CoV-2 virus, continues to evolve daily, age appears to be a primary risk factor for disease severity. Although children appear to have at least the same level of susceptibility to infection, they are less likely to suffer the severe consequences of SARS-CoV-2 infection, particularly to the extent seen in elderly patients. Before the rise of COVID-19, diagnosed viral sepsis constituted less than 1% of all cases. However, a compelling argument was recently made in *The Lancet* by Li and colleagues that severe and critically ill COVID-19 patients meet the Sepsis-3 diagnostic criteria for sepsis and septic shock [10].

As written by Joseph Heller in *Catch-22*, “The enemy is anybody who’s going to get you killed, no matter which side he’s on.” Indeed, this is the Catch-22 of sepsis: treatments must target excessive inflammatory amplification without frank toxicity or

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* Corresponding author.
E-mail address: vblaho@sbpdiscovery.org

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dampening the generation and maintenance of protective immunity to the initiating pathogen or secondary infections. The study by Weigel, et al. suggests modulating S1P degradation and signaling, pathways of ongoing pharmaceutical and clinical interest, as promising alternatives to toxic interventions in the inflammation amplification of sepsis.

Author contributions

V.A.B. was responsible for the literature search, data analysis and interpretation, and writing the manuscript.

Declaration of Competing Interest

The author declares no conflicting interests.

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